Three-Year Study of Estrogen Alone Versus Combined With Progestin in Postmenopausal Women With or Without Hypercholesterolemia

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This study compares the effects of long-term hormone replacement therapy on the lipid profile of postmenopausal women with or without hypercholesterolemia, with a comparison of 2 different regimens over a 3-year period. A total of 209 women were enrolled in this prospective, nonrandomized trial. They were classified into 2 groups according to baseline serum levels of total cholesterol and low-density lipoprotein (LDL) cholesterol. The hypercholesterolemic group consisted of 83 subjects with a total cholesterol level of 220 mg/dL or higher and LDL cholesterol 140 mg/dL or higher. The normocholesterolemic group consisted of 126 subjects with normal total and LDL cholesterol levels. Therapy was assigned as follows: 44 subjects in the hypercholesterolemic group and 67 in the normal cholesterol group with a total hysterectomy received conjugated equine estrogen (CEE) 0.625 mg/d, while 39 subjects in the hypercholesterolemic group and 59 in the normal cholesterol group with a physiological menopause received CEE 0.625 mg/d plus medroxyprogesterone acetate 2.5 mg/d. Fasting blood samples were monitored periodically for 3 years. Nine women withdrew from the study. Hormone replacement therapy had a more favorable effect in the hypercholesterolemic group versus the normal cholesterol group by decreasing total and LDL cholesterol, 7.0% and 16.6%, versus the normal cholesterol group, 0.8% and 3.9%. Serum levels of high-density lipoprotein (HDL) cholesterol were increased in both groups (hypercholesterolemic, 14.4%; normal cholesterol group, 26.5%), with the increase being larger in the normal cholesterol group. These changes were similar with both treatments and were maintained over 3 years. Serum levels of triglyceride were also increased in both groups, with the increase being statistically significant only in the group with normal cholesterol levels at baseline. There were no consistently reported side effects of therapy. The effects of postmenopausal hormone replacement therapy, estrogen with or without progestin, on the lipid profile appear to be related to the subject's baseline lipid values. Thus, such therapy may have a more favorable effect on LDL cholesterol in postmenopausal women with hypercholesterolemia, with the beneficial effect being maintained over 3 years.

POSTMENOPAUSAL WOMEN have an increased risk for coronary heart disease, consistent with their typically adverse serum lipoprotein profile.[1-3] Estrogen replacement therapy may have a beneficial effect in those with normal lipid levels by reducing the serum level of low-density lipoprotein (LDL) cholesterol and increasing the level of high-density lipoprotein (HDL) cholesterol.[4-6] The National Cholesterol Education Program Adult Treatment Panel II (NCEP ATPII) guidelines[7] suggest that estrogen replacement therapy be considered as a treatment option in postmenopausal women who show increased LDL cholesterol even after dietary therapy.

The administration of estrogen alone as hormone replacement therapy stimulates the endometrial lining of the uterus, and its long-term use is associated with a 4- to 8-fold increase in the risk of endometrial carcinoma.[8] This increased risk is significantly reduced when progestin is added to the treatment regimen. For this reason, postmenopausal women with an intact uterus are prescribed concomitant progestin to protect the endometrium.[9,10] However, there is a concern that the addition of progestin may reduce the cardioprotective effects of estrogen, especially its beneficial effect on lipoproteins.[11] Several studies[12,13] have demonstrated that the addition of medroxyprogesterone acetate does not reduce the effects of estrogen on the lipid profile. Other studies[14,15] have emphasized the beneficial effects of hormone replacement therapy in postmenopausal women with hypercholesterolemia. However, most of these studies were short-term investigations that did not compare the effects of therapy in subjects with normal cholesterol levels.

We have now evaluated whether a favorable effect of hormone replacement therapy is observed on the lipid profile of postmenopausal women with hypercholesterolemia during long-term treatment with estrogen with or without progestin. We compared the results obtained in subjects with hypercholesterolemia and subjects with normal cholesterol levels, with a comparison of the treatment regimens consisting of estrogen alone versus estrogen combined with progestin.

SUBJECTS AND METHODS

Subjects

A total of 209 postmenopausal Japanese women entered this prospective nonrandomized study. A total of 94 women (aged 46 to 67 years) with physiologic menopause and 115 women with surgically induced menopause due to bilateral oophorectomy (aged 40 to 53 years) were recruited from the menopause clinic at Hiroshima University Hospital. Subjects with physiologic menopause did not have a menstrual period during the preceding year. The surgically menopausal subjects underwent bilateral oophorectomy at least 1 year before the study. Menopausal status was confirmed by the demonstration of a serum concentration of follicle-stimulating hormone (FSH) greater than 40 mIU/mL and estradiol less than 20 pg/mL in each subject. None of the subjects smoked, used caffeine or alcohol regularly, or had a history of thyroid disease, liver disease, or diabetes mellitus. None had ever received hormone replacement therapy, other steroid hormones, or any medication known to affect lipoprotein metabolism.

The women enrolled in the study had a similar life-style and similar dietary habits—all were requested to avoid any changes in life-style and

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Submitted June 28, 1999; accepted December 3, 1999.

Supported in part by a Grant-in-Aid (09771279) for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

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0026-0495/00/4906-0020$10.00/0

doi:10.1053/meta.2000.6260

dietary habits during the investigation. All subjects provided informed consent for participation. The study protocol was approved by our institutional committee on ethical practice.

Study Design

To compare the effects of hormone replacement therapy on the lipid profile of postmenopausal women with or without hypercholesterolemia, the subjects were classified into 2 groups according to serum total cholesterol and LDL cholesterol levels at baseline. A total of 83 subjects with a total cholesterol of 220 mg/dL or higher and LDL cholesterol 140 mg/dL or higher were identified as the hypercholesterolemic group and compared with 126 subjects with normal levels of total and LDL cholesterol, ie, the normal cholesterol group. These classifications are in accordance with the Japan Atherosclerosis Society guidelines.

A total of 44 subjects in the hypercholesterolemic group and 67 in the normal cholesterol group received conjugated equine estrogen (CEE) 0.625 mg/d alone, while 39 subjects in the hypercholesterolemic group and 59 in the normal cholesterol group received CEE 0.625 mg/d plus medroxyprogesterone acetate 2.5 mg/d. Fasting blood samples were drawn after 6, 12, 18, 24, 30, and 36 months of each treatment.

Measurement of Lipids and Hormones

Blood samples were collected at baseline following a 12-hour fast. Blood was centrifuged immediately at 1,500 rpm for 20 minutes at 4°C to separate the serum for the assay of cholesterol, triglyceride, sex steroid hormones, urea, creatinine kinase, and liver function. Plasma concentrations of FSH and estradiol were measured by conventional radioimmunoassays. Serum levels of total cholesterol and triglyceride were measured by enzymatic methods.[16] HDL cholesterol was determined by precipitation and enzymatic methods.[17] The LDL cholesterol level was calculated using the Friedewald formula.[18]

Evaluation of Side Effects

We obtained a Papanicolaou smear, an endometrial biopsy, and a vaginal ultrasound sonogram to evaluate the thickness of the endometrium. A mammogram was obtained in each subject at baseline and every 6 months after starting treatment to detect the presence of mammitis or breast cancer.

Statistical Analysis

Data are reported at baseline and 12, 24, and 36 months after treatment. All data are presented as the mean ± SE. One-way ANOVA and the Student *t* test (unpaired) were used to compare differences between groups. Paired *t* tests were used to compare baseline and treatment values. Statview Software IV (Brainpower, Abacus Concepts) was used for all statistical procedures. Because of the multiple comparisons resulting from this study design, we also used repeated-measures multiple ANOVA to examine the overall effects of therapy over 3 years. A *P* value less than .05 was considered statistically significant.

RESULTS

A total of 209 women were enrolled in this study. A total of 200 subjects completed the study according to the protocol and were thus assessable (hypercholesterolemic group, n = 80; normal cholesterol group, n = 120). Three subjects in the hypercholesterolemic group withdrew from the study because of irregular bleeding. Six subjects in the normal cholesterol group withdrew, 4 for irregular bleeding and 2 for bloating and nausea. Baseline characteristics of the 2 study groups are shown in Table 1. There were no significant differences between the groups in age at study enrollment, age at menopause, years since menopause, height, body weight, body mass index, or plasma estradiol or FSH. Body weight did not change significantly in either group during the study. Baseline values for the lipid profile, total cholesterol, LDL cholesterol, HDL choles-

Table 1. Subject Characteristics, Plasma Sex Steroid Hormone Concentrations, and Lipid Profile

Parameter	Hypercholesterolemic Group (n = 80)	Normal Cholesterol Group (n = 120)
Age (yr)	53.3 ± 0.6	52.0 ± 0.6
Menopausal age (yr)	47.7 ± 0.5	46.3 ± 0.6
Years since menopause	5.7 ± 0.5	5.7 ± 0.5
Height (cm)	153.3 ± 0.6	154.8 ± 0.5
Weight (kg)	52.1 ± 0.8	51.9 ± 0.6
Body mass index (kg/m²)	22.2 ± 0.3	21.7 ± 0.2
FSH (mIU/mL)	51.0 ± 0.8	49.7 ± 0.5
Estradiol (pg/mL)	10.4 ± 0.8	11.4 ± 0.7
Total cholesterol (mg/dL)	246.1 ± 2.4*	191.1 ± 1.9
LDL cholesterol (mg/dL)	160.8 ± 2.8*	116.3 ± 2.2
HDL cholesterol (mg/dL)	60.1 ± 2.0*	54.1 ± 1.7
Triglyceride (mg/dL)	130.4 ± 4.5*	102.0 ± 6.0

NOTE. Hypercholesterolemic group: total cholesterol ≧220 mg/dL and LDL cholesterol ≧140 mg/dL. Normal cholesterol group: total cholesterol <220 mg/dL and LDL cholesterol <140 mg/dL. Data are the mean ± SE. One-way ANOVA was used to evaluate differences between the 2 groups.

*$P < .01$ *v* normal cholesterol group.

Table 2. Effects of Estrogen or Estrogen-Progestin Treatment in the Hypercholesterolemic Group

Parameter (mg/dL)	Estrogen Alone (n = 44)	Estrogen-Progestin (n = 36)
Total cholesterol		
Baseline	245.6 ± 3.7	246.7 ± 3.0
12 mo	226.0 ± 4.1*	218.9 ± 4.2*
24 mo	223.9 ± 4.2*	217.1 ± 4.2*
36 mo	232.8 ± 4.4*	222.7 ± 6.1*
LDL cholesterol		
Baseline	159.2 ± 3.9	162.6 ± 4.2
12 mo	135.9 ± 5.0*	133.1 ± 4.6*
24 mo	131.3 ± 4.6*	124.9 ± 4.4*
36 mo	135.1 ± 5.5*	131.2 ± 3.9*
HDL cholesterol		
Baseline	58.5 ± 2.7	62.0 ± 2.9
12 mo	61.8 ± 2.4†	63.8 ± 2.8†
24 mo	64.3 ± 3.0†	65.2 ± 2.4†
36 mo	65.4 ± 3.0*	68.2 ± 3.3*
Triglyceride		
Baseline	145.0 ± 13.0	112.4 ± 13.6
12 mo	141.9 ± 11.0	113.4 ± 10.0
24 mo	141.7 ± 13.9	129.4 ± 9.0
36 mo	151.0 ± 12.3	125.9 ± 10.2

NOTE. Estrogen treatment, CEE 0.625 mg daily. Estrogen-progestin treatment, CEE 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily. Data were obtained at baseline and at 12, 24, and 36 months after treatment and are presented as the mean ± SE. Paired *t* test was used between baseline values and values obtained at 12, 24, and 36 months after treatment.

*$P < .01$ *v* baseline.

†$P < .05$ *v* baseline.

terol, and triglyceride were significantly higher in the hypercholesterolemic group than in the normal cholesterol group ($P < .01$).

The hypercholesterolemic group showed a significant decrease in serum total and LDL cholesterol when the baseline value was compared with the 36-month value, 7.0% ($P < .01$) and 16.6% ($P < .01$), respectively. There were no significant differences between the 2 treatments in the ability to reduce serum cholesterol levels (estrogen treatment, total cholesterol 6.0% and LDL cholesterol 15.0%; estrogen-progestin treatment, total cholesterol 9.4% and LDL cholesterol 19.4%).

Compared with the baseline, serum HDL cholesterol in the hypercholesterolemic group showed a significant increase of 14.4% at 36 months. No significant difference was found between the 2 treatments (estrogen, 13.3%; estrogen-progestin, 13.4%). These favorable changes in lipids were first noted at 6 months and were maintained over the 3-year period. Compared with baseline, serum triglyceride levels were increased on both treatments by 10.2% and 14.1%, respectively, but these increases did not reach statistical significance (Table 2 and Fig 1).

The estrogen and estrogen-progestin treatments each increased the mean plasma estradiol concentration from 10.2 ± 0.8 pg/mL to 58.2 ± 4.8 pg/mL and from 11.8 ± 0.7 pg/mL to 52.6 ± 3.9 pg/mL by 6 months. These levels were maintained throughout the study. There was no significant difference between the 2 treatments.

In the group with normal cholesterol levels, serum LDL cholesterol decreased by 3.9% ($P < .05$), with no significant changes in serum total cholesterol, which probably reflected the greater increase in HDL cholesterol at 36 months. Although similar changes were observed on both treatments, the LDL cholesterol–lowering effect was less in the group with normal cholesterol levels at baseline versus the hypercholesterolemic group. In contrast, the serum level of HDL cholesterol increased by 28.2% on estrogen treatment and 25.3% on estrogen-progestin treatment at 36 months. A significant increase in serum triglyceride was also observed on both treatments (estrogen, 29.1%, $P < .01$; estrogen-progestin, 18.7%, $P < .05$). However, these increases were within the normal range (estrogen, from 101.1 ± 7.9 mg/dL to 128.3 ± 9.4 mg/dL; estrogen-

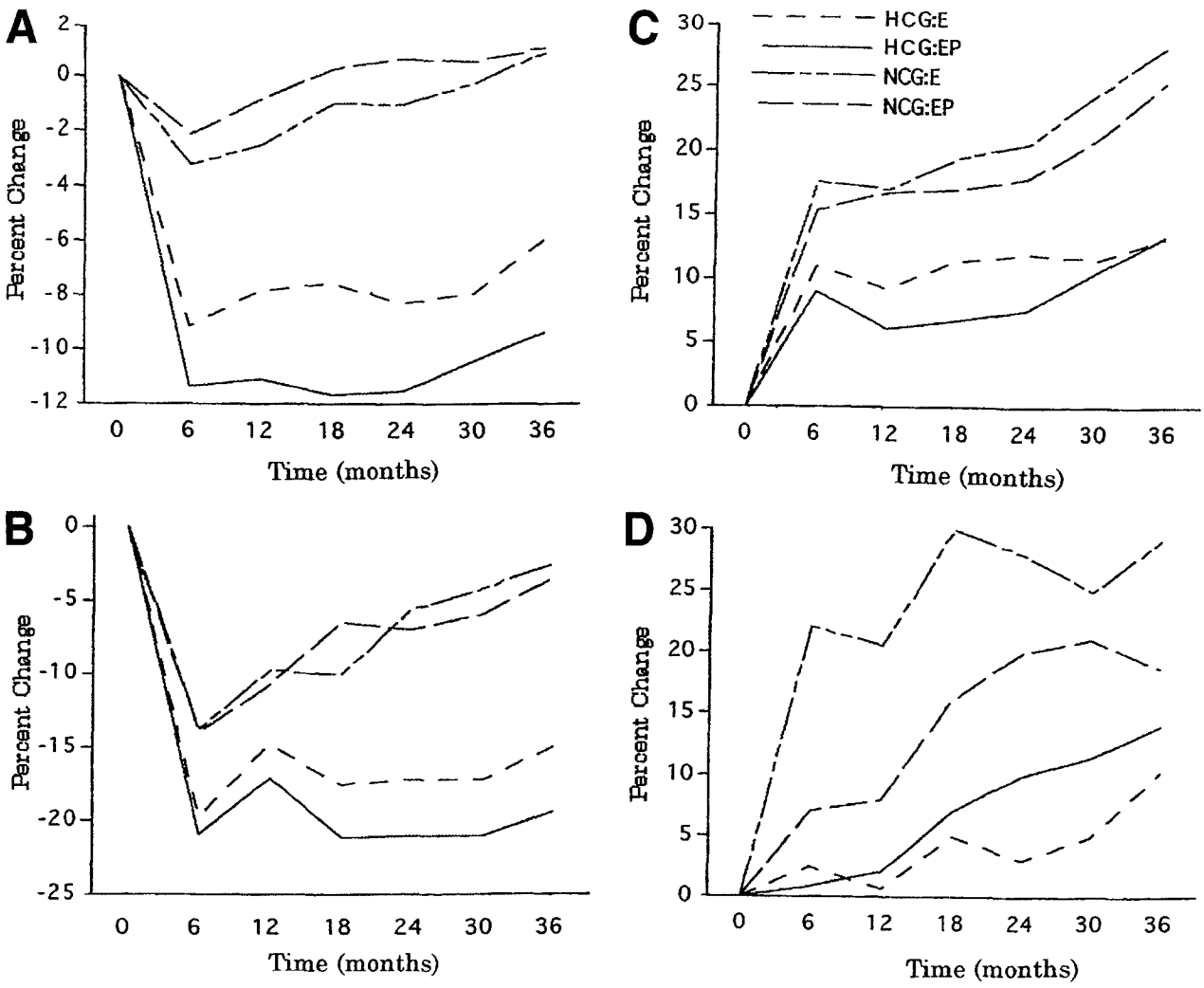

Fig 1. Mean percent change from baseline by treatment group for (A) total cholesterol, (B) LDL cholesterol, (C) HDL cholesterol, and (D) triglyceride. See Tables 1 and 2 for explanation of treatment groups. HCG, hypercholesterolemic group; NCG, normal cholesterol group; E, estrogen alone; EP, estrogen-progestin.

Table 3. Effects of Estrogen or Estrogen-Progestin Treatment in the Normal Cholesterol Group

Parameter (mg/dL)	Estrogen Alone (n = 67)	Estrogen-Progestin (n = 53)
Total cholesterol		
Baseline	190.3 ± 2.5	193.3 ± 2.7
12 mo	187.0 ± 3.4	188.0 ± 3.4
24 mo	194.8 ± 3.8	187.3 ± 3.3
36 mo	195.8 ± 3.6	195.4 ± 3.8
LDL cholesterol		
Baseline	115.1 ± 3.2	117.9 ± 2.9
12 mo	102.3 ± 3.8*	103.9 ± 3.5*
24 mo	106.1 ± 3.9†	100.0 ± 3.0*
36 mo	108.0 ± 3.9†	109.2 ± 4.4†
HDL cholesterol		
Baseline	52.8 ± 1.5	55.7 ± 1.8
12 mo	60.6 ± 1.8*	63.6 ± 2.1*
24 mo	63.0 ± 2.1*	63.7 ± 2.0*
36 mo	67.1 ± 2.1*	68.1 ± 2.1*
Triglyceride		
Baseline	101.0 ± 7.9	96.9 ± 9.0
12 mo	119.9 ± 7.8	96.1 ± 6.5
24 mo	131.0 ± 7.8*	111.0 ± 8.0†
36 mo	128.3 ± 9.4†	108.0 ± 6.5†

NOTE. Estrogen treatment, CEE 0.625 mg daily. Estrogen-progestin treatment, CEE 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily. Data were obtained at baseline and at 12, 24, and 36 months after treatment and are presented as the mean ± SE. Paired *t* test was used between baseline values and values obtained at 12, 24, and 36 months after treatment.

*$P < .01$ *v* baseline.

†$P < .05$ *v* baseline.

progestin, from 99.9 ± 9.0 mg/dL to 108.2 ± 6.5 mg/dL) (Table 3 and Fig 1).

We also found no statistically significant difference in mean plasma estradiol concentrations between the 2 treatments (estrogen, from 10.8 ± 0.5 pg/mL to 56.7 ± 3.1 pg/mL; estrogen-progestin, from 11.2 ± 0.4 pg/mL to 54.8 ± 3.3 pg/mL).

No side effects were consistently reported on either therapy. Three women in the hypercholesterolemic group showed mild and reversible elevations in serum aminotransferase, and 1 woman in the normal cholesterol group had a minor and reversible elevation of creatine kinase. No cases of abnormal endometrial histology indicating hyperplasia or carcinoma were detected in either group during the study. Two women in the normal cholesterol group developed mild and reversible mammitis, but we found no breast cancer.

DISCUSSION

The present study evaluates the effects of long-term hormone replacement therapy on the lipid profile of postmenopausal women with or without hypercholesterolemia, with a comparison of 2 different regimens over a 3-year period. Our results demonstrate that hormone replacement therapy appears to have a more favorable effect in postmenopausal women with hypercholesterolemia, with the beneficial effect being maintained over 3 years.

A recent meta-analysis of 34 protocols of continuous and sequential hormonal replacement therapy demonstrated some inconsistent findings, although in general, the effect of both regimens on lipid and lipoprotein levels was favorable.[19] The duration of treatment with combined continuous regimens was 3 to 36 months. Most studies were conducted for 12 months.

A few studies[14,15] have demonstrated the effects of postmenopausal hormone replacement therapy on lipoprotein levels in women with hyperlipidemia. However, these studies were also short-term and did not evaluate a control group of women with normal lipid levels.

The present study demonstrates the long-term effects of estrogen and estrogen-progestin on the lipid profile of postmenopausal women with or without hypercholesterolemia. An improvement in the lipid profile with beneficial effects was noted in the hypercholesterolemic group. Significant decreases were observed in total cholesterol and LDL cholesterol on each treatment at 12, 24, and 36 months as compared with baseline. No statistically significant differences were observed between the 2 treatments. While a significant decrease in LDL cholesterol was noted on both treatments in the normal cholesterol group, the decrease was less than that observed in the hypercholesterolemic group. No statistically significant change in the total cholesterol level was observed in the normal cholesterol group. These results suggest that the efficacy of hormone replacement therapy in decreasing serum levels of total and LDL cholesterol was greater in the hypercholesterolemic group versus the normal cholesterol group. The effects of such therapy on the lipid profile of postmenopausal women appeared according to their serum lipid levels at baseline.

While the NCEP ATPII[7] recommends estrogen replacement therapy as a treatment option in postmenopausal women with hypercholesterolemia, our data have shown that both estrogen and estrogen-progestin therapies may be useful in reducing cholesterol levels in postmenopausal women with hypercholesterolemia. Darling et al[20] have reported that estrogen-progestin therapy may be an effective alternative to treatment with simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor.

The present study showed a significant increase in HDL cholesterol in both groups, with the increase being larger in the group with normal cholesterol levels versus the group with elevated cholesterol. The baseline HDL cholesterol level in the normal cholesterol group was significantly lower than that in the hypercholesterolemic group (54.1 mg/dL *v* 60.1 mg/dL). In his review, Goldenberg[21] reported that hormone replacement therapy was more effective in treating postmenopausal women with a lower HDL cholesterol level. Our data support this finding.

In a comparison of treatment regimens, we found no difference in the increase of HDL cholesterol between the 2 treatments. The Postmenopausal Estrogen-Progestogen Intervention Trial (PEPI Trial),[22] a 3-year follow-up study, suggested that CEE given alone has a more favorable effect on the serum level of HDL cholesterol than the estrogen-progestin regimen. The reason for this difference between our results and the PEPI Trial is unclear. However, Nabulsi et al[23] showed that the use of conjugated estrogen and medroxyprogesterone acetate had either a slight effect or no effect on HDL cholesterol levels, in that medroxyprogesterone acetate has less influence than other progestins on hepatic lipase activity, which increases the catabolism of HDL2.[24] The present study demonstrated that the

addition of medroxyprogesterone acetate 2.5 mg/d had little or no effect on the level of HDL cholesterol.

Concerning the changes in serum triglyceride, a significant increase was observed in the normal cholesterol group, but not in the hypercholesterolemic group. Many studies[12,25,26] have shown that oral estrogen or estrogen-progestin treatments increase the serum level of triglyceride. However, most of these studies were performed in subjects with normal triglyceride levels at baseline. The effects of oral hormone replacement therapy in subjects with higher baseline triglyceride levels have not been fully evaluated. A case study[27] observed a reduction in triglyceride after estrogen treatment in patients with type III hyperlipidemia, due to an improvement in remnant (triglyceride-rich lipoprotein) metabolism. In the present study, the mean baseline triglyceride level in the hypercholesterolemic group, especially during estrogen treatment, exceeded that in the normal cholesterol group. The effect of hormone replacement on triglyceride metabolism may differ in patients with normal versus elevated triglycerides at baseline. In addition, the mean triglyceride level in the normal cholesterol group remained within the normal range throughout the study. Hypertriglyceridemia is a risk factor for cardiovascular disease because of the presence of lower HDL cholesterol or small dense LDL cholesterol.[28-30] However, according to the Japan Atherosclerosis Society guidelines, patients with a serum triglyceride level of 150 mg/dL or higher require such treatments as exercise, diet, or medication. Thus, we believe that the increase in serum triglyceride observed in the present study would have little effect on the development of cardiovascular disease.

In conclusion, the effects on the lipid profile of postmenopausal hormone replacement therapy, ie, estrogen given with or without progestin, appear to depend on the subject's lipid values at baseline. Therefore, hormone replacement therapy may have a more favorable effect on LDL cholesterol in postmenopausal women with hypercholesterolemia, with this beneficial effect being maintained over 3 years.

ACKNOWLEDGMENT

The authors thank Yoshiko Nakano for secretarial assistance.

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